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OCULOMOTOR AND PUPILLARY REFLEXES DURING ACUTE EXPOSURE TO HYPOBARIC HYPOXIA

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U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND

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13. ABSTRACT (Maximum 200 words) Unacclimatized military personnel rapidly ascending to high terrestrial elevations are likely to incur significant altitude illness. In an attempt to determine the identify physiological variables that may be associated with altitude-induced illness, we conducted two studies of pupillary/oculomotor responses (POR) to determine the effects of acute hypobaric hypoxic exposure, the reversibility of any effects with return to sea level, the possible impact of hypobaria, and the correlation of early heart rate changes and blood oxygen saturation values. The first study utilized a hypobaric chamber to determine whether POR were altered by acute hypobaric hypoxia and whether the effects, if any, were readily reversible. The second study was conducted on the summit of Pikes Peak to determine the relative role of hypobaria and the effects of a longer exposure. Saccadic velocity (SV), pupil diameter (PD), pupil constriction latency (CL), and pupil constriction amplitude (CL) were measured. In the chamber study, 26 healthy men and 9 women, aged 18 to 45 yrs, were gradually decompressed to 459 mmHg over 2.5 h. Heart rate and arterial oxygen saturation were measured by standard pulse oximetry. Within 1 h after reaching 459 mmHg, PD and CL were significantly reduced 5% and 2%, respectively. No changes were observed in CA or SV, nor were any differences found due to gender. In the Pikes Peak field study 18 men, aged 19-33, were driven to the summit (460 mmHg) breathing O2, tested, immediately retested without O2, and tested again 3 and 24 h later. Results were qualitatively similar to the hypobaric chamber study. No differences were found between measurements at sea level and O2 breathing at the summit. PD and CL decreased 12% and 5%, respectively, 3 h after termination of O2 breathing. Constriction amplitude also decreased 17% after 24 h exposure. A significant correlation was found between oxygen saturation and the change in PD. We conclude that PD, CL, and CA are likely affected by acute hypoxia rather than hypobaria and that these changes may reflect an effect on autonomic nervous system balance within the central nervous system that may be associated with subsequent altitude-induced illness.				
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BACKGROUND

Acute mountain Sickness (AMS) is a complex syndrome suffered by many unacclimatized, low-altitude residents who rapidly ascend to altitudes above 2,500 m. The illness can negatively impact any military mission at altitude that entails complex cognitive and physical tasks to the extent that the mission may be significantly compromised. However, AMS does not strike with equal ferocity or frequency in all individuals. Some individuals may be uniquely sensitive or insensitive. There is currently no means of accurately predicting into which category a single individual may fall, or of quantitating the severity of AMS by any means other than subjective questionnaire coupled a clinical assessment.

Over the years researchers have attempted to define the reasons for the varied susceptibility and also to identify potential risk factors. But, to date, no one has been able to predict, with reasonable certainty, who will become ill and to what extent. It has also been difficult to identify objective physiological variables that may be associated with illness. Without these relevant objective variables, research studies seeking to evaluate effective pharmaceutical or strategic beneficial interventions are decidedly more difficult. To be able to predict and quantify AMS in a more expeditious manner would be a distinct advantage, as it may eventually be possible to configure a military unit that would be able to function at altitude with minimal incapacitation by altitude illness. Achieving success in this goal would be accomplished by identifying simple, rapid, and objective physiological variables that are responsive to hypoxia – ones that follow the same temporal and quantitative pattern as reported AMS symptoms.

The purpose of this investigation was to evaluate the effects of acute exposures to moderate hypobaric hypoxia (~459 mmHg) on pupillary reflexes and oculomotor performance. A chamber and field study were performed to document the response, determine its reversibility, and discern the relative importance of hypobaria and hypoxia. It was hypothesized that pupillary and oculomotor responses would be altered within several hours of exposure to hypobaric hypoxia and that these changes would be reversible with return to sea level.

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EXECUTIVE SUMMARY

The current military is expected to incur significant altitude illness when units are rapidly exposed to terrestrial elevations exceeding 2,500 m. When incapacitating illness does occur, an increased burden is placed on unit medical and rescue/evacuation resources. This investigation evaluated the possibility that an easily administered test of pupillary/oculomotor responses could be used as a noninvasive, objective measure of the physiological impact of hypoxic exposure. The first phase of this project was a hypobaric chamber study to determine whether the test was responsive to acute hypobaric hypoxia. The second phase was a field study conducted on the summit of Pikes Peak to determine the effects of a slightly longer exposure and to determine the relative roles of hypobaria and hypoxia. A subsample of volunteers from the chamber study was also used to determine the reversibility of pupillary responses. Oculomotor performance and pupillary responses were correlated with resting heart rate and pulse oximetry values.

In a study investigating the effects of short exposures to simulated altitudes between 760 and 459 mmHg on heart rate and arterial blood oxygen saturation, 26 healthy men and nine women (mean: 26 yrs; range: 18 to 45 yrs) were exposed one time to a gradual decompression program that resulted in reaching 459 mmHg over a period of approximately 2.5 h. On a given exposure day, three or four volunteers were tested 7-10 times at sea level from 0800-0930 h, before initiation of decompression. All measurements were made within 1 h of reaching the 459-mmHg decompression level. Volunteers were tested using a FIT 2000 instrument that measured specific oculomotor and pupillary variables (saccadic velocity, pupil diameter, pupil constriction latency, and the amplitude of pupil constriction). In addition, heart rate and arterial oxygen saturation were measured by standard pulse oximetry. At 459 mmHg, pupil diameter and constriction latency were significantly reduced 5% and 2%, respectively. No changes were observed in constriction amplitude or saccadic velocity with simulated altitude, nor were any differences found due to gender. At simulated altitude but not at sea level, a negative relationship was found between constriction amplitude and age.

In a second study conducted on the summit of Pikes Peak (460 mmHg), 18 men (mean: 25 yrs; range: 19-33) were driven to the summit breathing O₂. They were tested immediately with and then without O₂, followed by further testing 3 and 24 h later. Results were qualitatively similar to the hypobaric chamber study. Pupil diameter and latency decreased 12% and 5%, respectively, 3 h after termination of O₂ breathing. Constriction amplitude also decreased 17% after 24 h exposure.

We conclude that pupil diameter, constriction latency, and constriction amplitude are affected by acute altitude exposure. The effects are readily reversible and probably not due to hypobaria. The fact that pupillary responses rather than saccadic velocity were significantly altered is indicative of a hypoxia-induced effect on autonomic nervous system balance within the central nervous system.

INTRODUCTION

Because of its strict reliance on a constant supply of oxygen and nutrients and the removal of waste products, the central nervous system (CNS) is particularly sensitive to diminution of the oxygen and nutrient supply and waste removal. When the ambient partial pressure of oxygen (PO_2) is diminished, as occurs with travel to moderate elevations, physiological responses are invoked in oxygen-sensing tissues that attempt to compensate for the reduction. Before acclimatization to altitude has progressed to a significant extent, sensitive individuals may endure a complex group of reversible, self-limited symptoms known as Acute Mountain Sickness (AMS) that can result in incapacitation and evacuation. Classically, AMS has been divided into cerebral and respiratory components. The cerebral component, as compared to the respiratory, is characterized by headache, anorexia, nausea, vomiting, insomnia, lassitude, ataxia, and malaise (8), and is currently quantified for research purposes using the Environmental Symptom Questionnaire (31, 32) or the Lake Louise Questionnaire (29).

Even though susceptibility to AMS is highly variable in an exposed population, it is generally believed that an individual's susceptibility is characteristic and reproducible. However, clear, concise, and objective measurements of AMS or predictors have yet to be identified even though many attempts have been made (1, 3, 7, 25, 26, 28, 30, 33). Noninvasive, objective CNS-related responses may offer a productive avenue for identifying hypoxia-sensitive and AMS-susceptible individuals and quantifying their degree of illness.

Of the special senses, vision is the most sensitive to hypoxia. For over 70 years, various parameters of visual performance have been studied with exposures to hypoxia (14, 15, 23, 24). These parameters include dark adaptation, night vision, central brightness contrast, and central acuity. These visual performance tests have a commonality in that they rely to a large extent on volunteer motivation and attention level. Visual tests that are independent of these factors offer a distinct advantage if they can be shown to relate to subsequent AMS, either as a predictor or a quantifier of severity. Such tests include oculomotor performance as measured by saccadic velocity and reflexes such as the pupillary response to a light flash. There is only sparse evidence, however, for an effect of hypoxia on pupillary reflexes (2, 13). Appenzeller et al. (2) found that pupil cycle time in a group ranging in age from 23 to 63 was increased when volunteers were exposed to 4,500 m altitude from 2,100 m. Thus, there is a justification for determining whether a CNS function that is not dependent on volunteer volition is affected by hypoxic exposure and is correlated to the susceptibility and severity of AMS.

It has been recognized for many years that altitude stimulates the sympathetic nervous system (4, 5, 20, 22). An increased role of the parasympathetic nervous system has also been suggested (9). Although resting blood levels of both epinephrine and norepinephrine rise with altitude exposure, the magnitude and time courses are different for the two catecholamines (19-21). Resting arterial epinephrine levels are

increased on arrival at altitude and fall toward sea-level values with acclimatization. Resting norepinephrine blood levels are increased several hours of exposure and remain elevated for several weeks.

Once the observation was made of the increases in urinary and plasma catecholamines with altitude exposure, attempts were made to relate autonomic nervous system function to altitude-induced illness and acclimatization with varied success (6, 10, 11, 17, 18). All of these studies assessed total sympathetic neuronal and adrenal medullary activity and thus related to overall systemic changes that may mask effects occurring at a more local level. For example, heart rate variability is a function of the intrinsic cardiac rhythm. This rhythm is modulated by circulating catecholamines and receptor site availability. It has been suggested that both the sympathetic and parasympathetic nervous systems are jointly involved in altitude acclimatization (12, 35). No attempt has been made to relate heart rate variability to AMS susceptibility or severity. Another modality modulated by the autonomic nervous system that has received little or no attention has been eye reflexes.

The elevated amounts of plasma and urinary epinephrine and norepinephrine measured at altitude are indicators of increased sympathetic activity. The elevated levels result primarily from the accumulation of unmetabolized catecholamines and spillover from neuronal terminals in sympathetic tissues or the adrenal medulla. Thus, plasma and urine levels provide a limited view of the possible systemic effects that these neurohumors have at peripheral nerve endings and end organs. The effects of an acute, transient, altitude-induced increase in epinephrine and a longer lasting, relatively larger increase in norepinephrine on pupillary responses and saccadic eye movements are unknown. If changes in pupillary responses are related to autonomic nervous system activity, and if sympathetic activity is related to susceptibility and severity of AMS as suggested (10, 11, 17, 18), then a simple, objective, and convenient physiological method will be available to assess AMS and altitude acclimatization.

The current report is based on data obtained from two studies: H98-09, A-8390, "Effect of residence at low and moderate altitudes on arterial oxygen saturation at moderate-to-high altitudes", and H02-01, A-11189, "Effect of increased energy expenditure, antioxidant intervention, and carbohydrate ingestion on work performance and acclimatization." Both studies allowed measurements of pupillary reflexes, saccadic velocity, and various physiological parameters to be made in a normal population of volunteers exposed to moderate hypobaric hypoxia. Pupillary and oculomotor measurements were compatible with the experimental designs and hypotheses of both studies.

OBJECTIVES

The primary objective of this report is to determine whether measures of oculomotor performance and pupillary reflexes are altered with acute exposure to hypobaric hypoxia and to rule out any effect that may be due to hypobaria *per se*. Secondly, we hope to demonstrate the reversibility of any changes with return to sea

level and normalization of oxygen pressure. Other objectives are to determine whether any effects correlated with early heart rate and blood oxygen saturation values.

METHODS

STUDY DESIGN AND SIMULATED ALTITUDE ASCENT

As part of a research protocol investigating the effects of staging on heart rate and arterial blood oxygen saturation, 35 healthy U.S. Army enlisted soldiers and officers (26 healthy men and 9 women) were exposed on one occasion to a gradual decompression schedule (Table 1). Initially, the hypobaric chamber was decompressed at a rate that simulated an ascent rate of 1,000 ft/min to an altitude of 7,000 ft (582 mmHg). Chamber conditions were maintained at 20°C and 45% relative humidity. Illumination level within the chamber was maintained at 237 lux. After 10 min at 7,000 ft simulated altitude, the chamber was further decompressed at a rate of ~180 ft/min, which closely approximated an actual ascent rate up the Pikes Peak toll road. Additional ascent plateaus were maintained for 15-20 min at 560, 521, and 484 mmHg, with the final pressure of 459 mmHg (~13,318 ft) attained after 4.2 h. Almost all eye measurements were made within 1 h after attaining 459 mmHg. Volunteers remained at 459 mmHg approximately 90 min. The chamber was recompressed back to ambient sea-level pressure at a rate of 500 ft/min. Total time for chamber decompression and recompression was approximately 5.7 h.

At sea level, prior to decompression, volunteers were familiarized with all the procedures. Volunteers repeated the pupillary and saccadic velocity tests a total of 10 times in order to establish an individual baseline. On a given exposure day, 3 or 4 volunteers were tested from 0800-0930 h before initiation of chamber decompression. Oculomotor measurements and pupillary reflexes were obtained from 5 volunteers immediately after return to sea level.

INSTRUMENTATION

Oculomotor and pupillary reflexes were made using the FIT 2000 (PMI, Inc., Rockville, MD). The Fit 2000 is a self-contained, fully automated Class I medical instrument designed to analyze the eye reflexes for signs of neurological changes due to a variety of positive or negative stimuli. The instrument can detect changes as small as 0.05 mm in pupil size and eye movements as small as one degree. Saccadic velocity, pupil diameter, pupil constriction latency to a flashing light, and the pupil constriction amplitude were measured in a volunteer's dominant eye at least 2-4 min apart for a total of 10 times at sea level and 5 times at simulated altitude. To evoke a pupil reflex, 4-7 controlled, one-second flashes of light were produced that were constant regardless of pupil size. To evoke a measured saccadic eye movement, a

lighted target moved along a precise horizontal path that the volunteer followed with his/her dominant eye. The entire test took ~30 s to complete.

Blood oxygen saturation (SaO₂) and heart rate (HR) were measured by pulse oximetry (Nellcor N-200, Nellcor Inc., Pleasanton, CA) after the volunteers were seated and resting for 10 min.

RESULTS

VOLUNTEER PHYSICAL CHARACTERISTICS

The age and eye dominance for the men and women volunteers in the simulated altitude study and Pikes Peak study are presented in Table 1. There were no effects of gender on oculomotor or pupillary reflexes. Table 1 indicates the distribution of men to women and the distribution of individuals with right or left eye dominance. Volunteers did not differ with respect to whether they were right or left eye dominant. There was borderline significance ($p=0.049$) obtained with respect to constriction amplitude and age, but the result was only obtained at altitude. Constriction amplitude appears to decrease with age. No other measured variable significantly correlated with age.

Table 1 shows the distribution of males to females and their ages for the simulated altitude study. Only males were tested for the Pikes Peak study. There was no effect of eye dominance on any of the variables measured.

Table 1. Age and eye dominance of volunteers

Group	Age (yrs)	Eye Dominance	
		Left	Right
Hypobaric Chamber – Simulated Altitude			
Males (n=26)	25 ± 2	10	16
Females (n=9)	29 ± 4	4	5
COMBINED	26 ± 6	14	21
Pikes Peak			
Males (n=18)	25 ± 1	5	13

Values are means ± SE

RESPONSES DURING SIMULATED ALTITUDE EXPOSURE

The values in Table 2 are within the limits for a sea-level population published by PMI, Inc. Twenty-nine of 35 volunteers decreased their pupil diameter after less than 1 h of altitude exposure to 459 mmHg. The mean decrease from sea level in pupil diameter was 8.2% (max: 23.6%; min: 0.1%). However, because the staging protocol required resting at higher pressures for short periods of time, the total time exposed to hypobaric hypoxia was approximately 2.5-3 h.

Table 2. Means and variability for pupillary reflexes and oculomotor performance for hypobaric chamber study

	Sea Level			
	Pupil Diameter mm	Constriction Amplitude mm	Constriction Latency msec	Saccadic Velocity mm·sec ⁻¹
Mean	6.0	1.3	302	72
S.D.	1.0	0.3	26	7
S.E.	0.2	0.1	4	1
Max.	7.8	1.9	359	85
Min.	3.7	0.6	265	52
C.V.	16	26	9	10
	Simulated Altitude			
	Pupil Diameter mm	Constriction Amplitude mm	Constriction Latency msec	Saccadic Velocity mm·sec ⁻¹
Mean	5.7*	1.3	296**	72
S.D.	1.0	0.3	27	8
S.E.	0.2	0.1	5	1
Max.	7.5	1.9	358	89
Min.	3.5	0.8	248	54
C.V.	16	25	9	11

Sea-level mean values for 35 volunteers were calculated from 10 repetitions; simulated altitude (<1h, 459 mmHg) mean values for each volunteer were calculated from 5 repetitions. †The data for the "Return to sea level" were taken from a subsample of 5 subjects. S.D. = standard deviation; S.E. = standard error; Max. = maximum; Min. = minimum; C.V. = coefficient of variation. * P<0.001; **P=0.001.

Five volunteers were randomly chosen during one exposure period to determine the lability of the change observed in the pupil diameter with acute hypobaric hypoxic exposure (Table 3). Although pupil diameter decreased 9% (p=0.001) within 1 h of attaining 459 mmHg, within 0.5 h of return to sea level, values returned to within 97% of the pre-exposure sea-level value. Values still remained significantly different from those obtained at 459 mmHg (p=0.02). All other variables, i.e., constriction latency, constriction amplitude, and saccadic velocity, were unaltered at altitude and after return to sea level.

Table 3. Means and variability for pupillary reflexes and oculomotor performance for hypobaric chamber study on a subsample of 5 volunteers, with measurements made upon return to sea level

	Sea Level			
	Pupil Diameter mm	Constriction Amplitude mm	Constriction Latency msec	Saccadic Velocity mm·sec ⁻¹
Mean	5.9	1.0	300	71
S.D.	1.1	0.1	12	8
S.E.	0.5	0.1	5	3
Max.	7.8	1.2	314	78
Min.	5.0	0.9	282	61
C.V.	19	13	4	11
Simulated Altitude				
Mean	5.4*	0.9	297	69
S.D.	1.1	0.1	13	6
S.E.	0.5	0.0	6	3
Max.	7.3	1.1	309	77
Min.	4.7	0.8	277	62
C.V.	21	12	4	9
Return to Sea Level [†]				
Mean	5.7	1.1	306	67
S.D.	1.0	0.1	15	7
S.E.	0.5	0.0	7	3
Max.	7.84	1.2	319	73
Min.	5.0	0.9	280	58
C.V.	18	10	5	11

S.D. = standard deviation; S.E. = standard error; Max. = maximum; Min. = minimum; C.V. = coefficient of variation. * P=0.001; **P=0.02. [†] = compression occurred at a rate of 500 ft/min; all measurements were obtained within 0.5 h of return to sea-level ambient pressure.

RESPONSES DURING PIKES PEAK EXPOSURE

Table 4. indicates there was no reduction in pupil diameter immediately after arriving at the Pikes Peak summit with or without supplemental oxygen. Nor was there a reduction after 30 min after removing supplemental O₂. The first indication of a reduction in pupil diameter occurred after 3 h (p<0.001). Unlike the hypobaric chamber study where hypoxia was induced on a relatively gradual basis, abrupt exposure to hypoxia at Pikes Peak resulted in a decrease in constriction amplitude after 3 h. Slight changes in constriction latency began after 3 h (nonsignificant) and became evident after 24 h (p<0.001). There was no change in saccadic velocity at any time.

Table 4. Mean (\pm S.E.) of pupillary reflexes and oculomotor performance of 18 male volunteers at sea level (Palo Alto, CA) and the summit of Pikes Peak, CO (PP, 463 mmHg)

Variable	Environmental Condition				
	Sea Level	PP+O ₂	PP 0h	PP 3h	PP 24h
Pupil Diameter (mm)	5.9 \pm 0.2	5.9 \pm 0.2	5.8 \pm .2	5.2 \pm 0.3**	5.3 \pm 0.2**
Constriction Amplitude (mm)	1.23 \pm 0.06	1.23 \pm 0.11	1.22 \pm 0.05	1.02 \pm 0.06 *	1.05 \pm 0.07 *
Constriction Latency (msec)	295 \pm 3	302 \pm 5	297 \pm 4	292 \pm 5***	286 \pm 5**
Saccadic Velocity (mm·sec ⁻¹)	69 \pm 2	68 \pm 3	70 \pm 3	69 \pm 3	72 \pm 2

Volunteers received O₂ the evening prior to and during the first measurement (PP+O₂) that occurred within 0.5 h of attaining the summit. PP 0h = 30 min without supplemental O₂.

* p=0.01 compared to sea level or PP+O₂

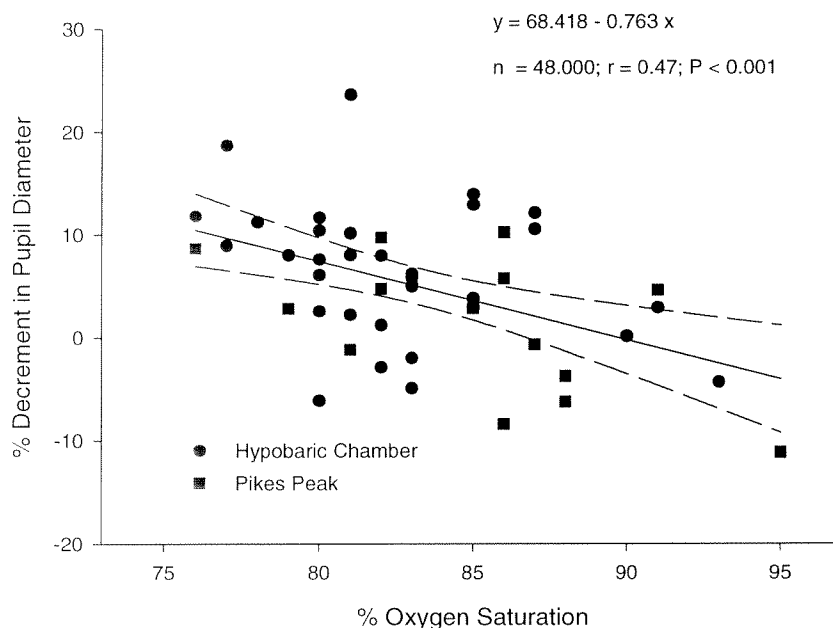
** p<0.001 compared to sea level or PP+O₂

*** p=0.058 compared to PP+O₂

RELATIONSHIP OF PUPIL DIAMETER CHANGE WITH HYPOXIA AND OXYGEN SATURATION

Figure 1 depicts the significant relationship between the decrease in pupil diameter and the percentage oxygen saturation from both the hypobaric chamber study and the Pikes Peak study. Mean saturation for the chamber study was 82.6 ± 0.6 mmHg, and for the Pikes Peak exposure was $85.8 \pm 1.2\%$. Pupil and pulse oxygen saturation measurements were separated by no more than 1 h. The larger the change in pupil diameter, the lower was the percentage oxygen saturation. Of the 48 volunteers represented in Figure 1, 31 (77%) had decreases in pupil diameter within 3 h of exposure to their maximum altitude exposure. There were no significant changes in constriction latency, constriction amplitude, or saccadic velocity associated with the level of oxygen saturation.

Figure 1. Dependence of pupil diameter on pulse oxygen saturation



DISCUSSION

The objective of the present report was to determine the effect of an acute exposure to simulated and real high altitude on oculomotor performance and pupillary

reflexes. To that end, two studies were conducted that measured pupil diameter, pupillary latency and constriction amplitude to light flashes, and saccadic velocity. Measurements during the first study were made within 1 h of attaining the simulated summit of Pikes Peak, preceded by a slow 2.5-h staged ascent. On the second study, volunteers breathed 100% O₂ the evening before and during an auto ascent of Pikes Peak. They were tested immediately upon attaining the summit while breathing supplemental O₂ and periodically afterwards while breathing ambient O₂.

Both studies resulted in significant reductions in pupil diameter within 3 h of exposure to hypoxia. With the longer exposure times available at Pikes Peak, significant reductions were also found in constriction amplitude and latency. Saccadic velocity was not affected on either study. Within 0.5 h of returning to sea-level oxygen pressures, pupil diameter returned to normal. This would indicate that the effect is readily reversible, at least when the hypoxia is not of long duration. It is not known whether the effects would persist with continued exposure and would be reversible with administration of O₂.

Because of the changes in both partial pressure of oxygen and the barometric pressure in the chamber study, the question arose as to whether the observed results could be attributed solely to changes in ambient barometric pressure. This question is at least partially answered by having the Pikes Peak volunteers continuously breathe 100% O₂ after arrival in Colorado Springs, CO, during, and immediately after automobile ascent to the summit while being subjected to barometric pressures ranging from 609-460 mmHg. The Pikes Peak group received supplemental O₂ until they completed their first set of tests on the summit. Since there were no differences in any variable while breathing O₂ on the summit or immediately after removal of the supplemental O₂ when compared to sea level, we conclude that at least 1-3 h of hypoxia are necessary to effect a pupillary change and that several hours hypobaria *per se* were inconsequential. The directions of the observed changes, however, were contrary to those we expected. That is, instead of dilation of the pupil, which would occur with stimulation by the sympathetic nervous system (SNS), we found that most volunteers' pupils contracted.

One possible explanation may be as follows. The muscles of the pupil are innervated by the autonomic nervous system, with adrenergic impulses to the radial muscle of the iris causing contraction (mydriasis or pupil widening) and cholinergic impulses to the iris sphincter muscle produce contraction resulting in miosis (narrowing of the pupil). Because hypoxic exposures lasting several days or weeks are associated with a stimulation of the SNS (20, 22), we expected changes in pupillary reflexes to be consonant with increased SNS activity. Thus, hypoxic exposure should have caused pupillary dilation.

The increase in hypoxia-induced SNS activity has usually been assumed to occur because of increased concentrations of catecholamines in plasma and urine, a reflection of the overflow from peripheral nerve endings. However, it is possible that

another sequence of events occurs in the CNS. A healthy iris is in constant motion even when light conditions and accommodation are constant. This physiologic pupillary instability or dynamic equilibrium is presumed to be due to fluctuations in the activity of sympathetic and parasympathetic innervations to the iris muscles. As explained by Thompson (34), when an individual's level of consciousness or alertness is reduced, as may occur with hypoxia, his pupils become smaller and also begin to oscillate. This is a reflection of a decrease in inhibition of the Edinger-Westphal nucleus, a parasympathetic component of the oculomotor nucleus, followed by a preponderance of parasympathetic outflow. This results in miosis (16).

There is further evidence for a reduction in pupil size with a decrease in level consciousness, alertness, and hypoxia. Morad et al. (27) observed decreases in pupil size with fatigue and subjective feelings of sleepiness. An early study of pupil size taken during anesthesia and respiratory insufficiency assumed that dilation would result from decreases in arterial PO_2 . However, within minutes of anoxic episodes resulting in arterial PO_2 's as low as 34 mmHg, either no change or contraction was observed, contrary to what was expected (13). Appenzeller et al. (2) found an increase in pupil cycle time, a measure of autonomic function, at 4500 m altitude. They erroneously associated the increase with the previous observation of an altitude-induced increase in circulating catecholamines, but this would have resulted in pupil widening. Pupils begin to oscillate when a volunteer is fatigued and pupils are small (34).

We demonstrated a significant inverse relationship between percentage of oxygen saturation and the change in pupil diameter. Those volunteers with lower saturations at altitude had greater reductions in pupil diameter. We did not test a possible correlation with the incidence or severity of AMS. However, recent studies have shown a link between the development of AMS and low blood oxygen saturation whether produced by hypoventilation or impaired gas exchange (1, 7, 26, 33). Therefore, it is conceivable that pupil diameter changes at altitude may be related to the development of AMS. That this relationship can be easily and quickly measured may provide a tool with which volunteers may be differentiated into groups that are hypoxia-sensitive/hypoxia-resistant or AMS-susceptible/AMS-resistant.

CONCLUSIONS

Within a few hours of exposure to hypobaric hypoxia, discernible changes can be measured in specific pupillary reflexes. These changes were probably not affected by changes in barometric pressure and were readily reversed when exposure lasted only a few hours. The fact that pupillary responses, rather than saccadic velocities, were affected is consistent with the concept that the initial few hours of exposure to hypoxia are associated with a reduction in parasympathetic inhibition of oculomotor neurons within the CNS. The inverse relationship of pupillary change and oxygen saturation may be a means of identifying AMS susceptible individuals after a short exposure to hypoxia.

REFERENCES

1. Anholm, J. D., C. S. Houston, and T. M. Hyers. The relationship between acute mountain sickness and pulmonary ventilation at 2,835 meters (9,300 ft). *Chest* 75: 33-36, 1979.
2. Appenzeller, P., O. Appenzeller, and S. Wood. Pupil cycle time, aging, and altitude exposure. In: *Hypoxia and Mountain Medicine*, edited by J. R. Sutton, G. Coates, and C. S. Houston. Burlington: Queen City Printers, 1992, p. 298.
3. Bärtsch, P., N. Pflüger, M. Audétat, S. Shaw, P. Weidmann, P. Vock, W. Vetter, D. Rennie, and O. Oelz. Effects of slow ascent to 4559 m on fluid homeostasis. *Aviat. Space Environ. Med.* 62: 105-110, 1991.
4. Becker, E. J., and F. Kreuzer. Sympathoadrenal response to hypoxia. *Pflügers Arch.* 304: 1-10, 1968.
5. Cunningham, W. L., E. J. Becker, and F. Kreuzer. Catecholamines in plasma and urine at high altitude. *J. Appl. Physiol.* 20: 607-610, 1965.
6. Fulco, C. S., P. B. Rock, J. T. Reeves, L. A. Trad, P. M. Young, and A. Cymerman. Effects of propranolol on acute mountain sickness (AMS) and well-being at 4,300 meters of altitude. *Aviat. Space Environ. Med.* 60: 679-683, 1989.
7. Hackett, P. H., D. Rennie, S. E. Hofmeister, R. F. Grover, E. B. Grover, and J. T. Reeves. Fluid retention and relative hypoventilation in acute mountain sickness. *Respir.* 43: 321-329, 1982.
8. Hackett, P. H. and R. C. Roach. High-altitude medicine. In: *Wilderness Medicine: Management of Wilderness and Environmental Emergencies*, edited by P. S. Auerbach. St. Louis: Mosby-Year Book, Inc., 2001, p. 2-43.
9. Hartley, L. H., J. A. Vogel, and J. C. Cruz. Reduction of maximal exercise heart rate at altitude and its reversal with atropine. *J. Appl. Physiol.* 36: 362-365, 1974.

10. Hoon, R. S., S. C. Sharma, V. Balasubramanian, and K. S. Chadha. Urinary catecholamine excretion on induction to high altitude (3,658 m) by air and road. *J. Appl. Physiol.* 42: 728-730, 1977.
11. Hoon, R. S., S. C. Sharma, V. Balasubramanian, K. S. Chadha, and O. P. Mathew. Urinary catecholamine excretion on acute induction to high altitude (3,658 m). *J. Appl. Physiol.* 41: 631-633, 1976.
12. Hughson, R. L., Y. Yamamoto, R. E. McCullough, J. R. Sutton, and J. T. Reeves. Sympathetic and parasympathetic indicators of heart rate control at altitude studied by spectral analysis. *J. Appl. Physiol.* 77: 2537-2542, 1994.
13. Jordanov, J., and H. Ruben. Reliability of pupillary changes as a clinical sign of hypoxia. *Lancet* 2: 915-917, 1967.
14. Kobrick, J. L. Effects of exposure to 12,800 feet and acetazolamide on visual performance. *Percept. Mot. Skills* 27: 939-944, 1968.
15. Kobrick, J. L., H. Zwick, C. E. Witt, and J. A. Devine. Effects of extended hypoxia on night vision. *Aviat. Space Environ. Med.* 55: 191-195, 1984.
16. Lowenstein, O., R. Feinberg, and I. E. Loewenfeld. Pupillary movements during acute and chronic fatigue: a new test for the objective evaluation of tiredness. *Invest. Ophthalmol.* 2: 138, 1963.
17. Malhotra, M. S., W. Selvamurthy, S. S. Purkayastha, A. K. Mukherjee, L. Mathew, and G. L. Dua. Responses of the autonomic nervous system during acclimatization to high altitude in man. *Aviat. Space Environ. Med.* 47: 1076-1079, 1976.
18. Mathew, L., S. S. Purkayastha, A. Jayashankar, U. Radhakrishnan, J. Sen Gupta, and H. S. Nayar. Responses of the autonomic nervous system in altitude adapted and high altitude pulmonary oedema subjects. *Int. J. Biometeorol.* 29(2): 131-143, 1985.
19. Mazzeo, R. S. Pattern of sympathoadrenal activation at altitude. In: *Hypoxia and Molecular Medicine*, edited by J. R. Sutton, C. S. Houston, and G. Coates. Burlington: Queen City Printers, Inc., 1993, p. 53-61.

20. Mazzeo, R. S., P. R. Bender, G. A. Brooks, G. E. Butterfield, B. M. Groves, J. R. Sutton, E. E. Wolfel, and J. T. Reeves. Arterial catecholamine responses during exercise with acute and chronic high-altitude exposure. *Am. J. Physiol.* 261: E419-E424, 1991.
21. Mazzeo, R. S., A. Child, G. E. Butterfield, J. T. Mawson, S. Zamudio, and L. G. Moore. Catecholamine response during 12 days of high-altitude exposure (4,300 m) in women. *J. Appl. Physiol.* 84: 1151-1157, 1998.
22. Mazzeo, R. S., E. E. Wolfel, G. E. Butterfield, and J. T. Reeves. Sympathetic response during 21 days at high altitude (4,300 m) as determined by urinary and arterial catecholamines. *Metabolism* 43: 1226-1232, 1994.
23. McFarland, R. A. Anoxia: Its effect on the Physiology and Biochemistry of the brain and on behavior. In: *The Biology of Mental Health and Disease*, New York: P.B. Hoeber Inc., 1952, p. 335-355.
24. McFarland, R. A., J. N. Evans, and M. H. Halperin. Ophthalmic aspects of acute oxygen deficiency. *Am. J. Ophthalmol.* 26: 886-913, 1941.
25. Milledge, J. S. Salt and water control at altitude. *Int. J. Sports Med.* 13 Suppl 1: S61-S63, 1992.
26. Moore, L. G., G. L. Harrison, R. E. McCullough, R. G. McCullough, A. J. Micco, A. Tucker, J. V. Weil, and J. T. Reeves. Low acute hypoxic ventilatory response and hypoxic depression in acute altitude sickness. *J Appl. Physiol* 60: 1407-1412, 1986.
27. Morad, Y., H. Lemberg, N. Yofe, and Y. Dagan. Pupillography as an objective indicator of fatigue. *Curr. Eye Res.* 21: 535-542, 2000.
28. Reeves, J. T., L. G. Moore, R. E. McCullough, R. G. McCullough, G. Harrison, B. I. Tranmer, A. J. Micco, A. Tucker, and J. V. Weil. Headache at high altitude is not related to internal carotid arterial blood velocity. *J Appl. Physiol* 59: 909-915, 1985.
29. Roach, R. C., P. Bärtsch, O. Oelz, and P. Hackett. The Lake Louise acute mountain sickness scoring system. In: *Hypoxia and Molecular Medicine*, edited by J. R. Sutton, C. S. Houston, and G. Coates. Burlington: Queen City Press, 1993, p. 272-274.

30. Roach, R. C., E. R. Greene, R. B. Schoene, and P. H. Hackett. Arterial oxygen saturation for prediction of acute mountain sickness. *Aviat. Space Environ. Med.* 69: 1182-1185, 1998.
31. Sampson, J. B., A. Cymerman, R. L. Burse, J. T. Maher, and P. B. Rock. Procedures for the measurement of acute mountain sickness. *Aviat. Space Environ. Med.* 54: 1063-1073, 1983.
32. Sampson, J. B., and J. L. Kobrick. The environmental symptoms questionnaire: revisions and new field data. *Aviat. Space Environ. Med.* 51: 872-877, 1980.
33. Sutton, J. R., A. C. Bryan, G. W. Gray, E. S. Horton, A. S. Rebuck, W. Woodley, I. D. Rennie, and C. S. Houston. Pulmonary gas exchange in acute mountain sickness. *Aviat. Space Environ. Med.* 47: 1032-1037, 1976.
34. Thompson, H. S. The pupil. In: *Adler's Physiology of the Eye*, edited by R. A. Moses. St. Louis: C.V. Mosby Co., 1981, p. 326-356.
35. Wolfel, E. E., M. Meertens, J. Tokeshi, et al. Diminished sympathetic and preserved para-sympathetic activity with alpha-adrenergic blockade in women at high altitude. *Advances in Experimental Medicine and Biology* 474: 441, 1999.